

## Remarks

### *Status of the Claims*

Claims 1-4 are pending.

By the above amendment, claims 5-19 have been canceled without prejudice to the right to pursue them in a divisional application.

Claim 1 has been rewritten to more clearly indicate that RNA preservation is accomplished by an RNA precipitating step that comprises contacting the biological sample with an aqueous solution comprising an RNA preservative, whereby the precipitated RNA is retained with the biological sample through the histochemical staining and histochemical analyzing steps. The amendment is supported in the specification as originally filed, for example, at page 22, lines 6 through 14, and page 33, line 6, through page 35, line 8. Thus, the amendment introduces no new matter.

### *Response to Restriction Requirement*

In the outstanding Office Action, the Examiner required restriction under 35 U.S.C. § 121 to one of the following inventions: (I) claims 1-4; and (II) claims 5-19. Applicant hereby affirms the election of Group I, claims 1-5. This election is without traverse insofar as the groups of claims are directed to patentably distinct inventions. Accordingly, non-elected claims 5-19 have been canceled.

### *Claims 1-4 Are Patentable Under 35 U.S.C. § 103(a)*

In the outstanding Office Action, the Examiner rejected claims 1-4 under 35 USC § 103(a) as being unpatentable over Rimm et al. (US 2002/0177149) in view of Reiter et al. (US 2002/0102666). The Examiner additionally rejected claim 2 as being unpatentable over Rimm et al. (US 2002/0177149) in view of Reiter et al. (US 2002/0102666), and further in view of Lader (US 6,204,375) and/or Willson III et al. (US 2002/0197637). These rejections are respectfully traversed.

Claim 1 is directed to a method of analyzing a biological sample comprising precipitating RNA in the biological sample by contacting the biological sample with an

aqueous solution comprising an RNA preservative, histochemically staining and analyzing the biological sample, where the RNA is preserved within the biological sample through the histochemical staining and analysis, and analyzing mRNA expression patterns of identified cells by a method comprising in-situ hybridization or isolating identified cells and subjecting the isolated cells to bioarray gene profiling. Dependent claims 2 and 3 further recite the use of preferred RNA preservatives and dependent claim 4 further recites the use of preferred histochemical analysis embodiments.

In rejecting the claims the Examiner argued that the primary reference, Rimm et al., teaches a method of analyzing a biological sample comprising all of the features in claim 1, except for histochemical analysis of the biological sample to identify specific cell populations. Applicant respectfully submits that the Examiner has mischaracterized the teachings of the primary reference.

The Rimm et al. reference describes methods for automated optical analysis of preparations of cell-containing samples to visualize and quantitate biomarkers within such samples. The primary reference discloses myriad reagents used as histological stains, counterstains, chromophores, fluorophores for detection of target cells, cellular components, or subcellular structures (see paragraphs 0085 through 0105), which may be employed in the processing of biological samples for optical analysis. The reference provides no teaching or suggestion of precipitating RNA in a biological sample by contacting the biological sample with an RNA preservative in an aqueous solution as recited in present claims, where the thus-preserved RNA is retained within the biological sample throughout subsequent histochemical staining and histochemical analyzing steps.

The Reiter et al. reference fails to cure the deficiencies of the primary reference. The Examiner cited the secondary reference for its alleged teaching of identification of cancer cells that overexpress PSCA mRNA via *in situ* hybridization. The Reiter et al. reference, however, fails to teach or suggest precipitating RNA in a biological sample by contacting it with an aqueous solution comprising an RNA preservative, followed by histochemical staining and histochemical analysis, whereby the precipitated RNA is

preserved within the biological sample through histochemical staining and histochemical analyzing steps. Thus, the combined teachings of Rimm et al. and Reiter et al. would not have motivated a person of ordinary skill in the art to arrive at the claimed method.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination. ACS Hosp. Systems, Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984)). Since the Rimm et al. and Reiter et al. references fail to provide the necessary teachings and suggestions so as to arrive at each claimed feature of Applicant's invention, the rejection fails to set forth a proper *prima facie* case of obviousness.

The error in the rejection is reflected by the Examiner's failure to cite specific passages in the references providing an explicit or implicit teaching or suggestion for arriving at a method comprising each claim feature, including an RNA-preserving precipitation step prior to histochemical staining and analysis. When the USPTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears in the reference. In re Rijckaert, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

The fallaciousness of the rejection is further reflected by the Examiner's reliance on the concept of inherency in an attempt to arrive at the claimed precipitation step. In particular, "[a]s regards the limitation in Claim 1 which reads 'so as to precipitate RNA' the examiner contend[ed] that this limitation is inherent to both of Rimm et al. and Reiter et al." (Office Action, p. 4). The inherency of an advantage and its obviousness, however, are entirely different questions. In re Naylor, 360 F.2d 765, 152 U.S.P.Q. 106 (CCPA 1966); *see also* In re Shetty, 566 F.2d 81, 195 USPQ 753 (CCPA 1977).

Thus, the Examiner's inherency argument is predicated on nothing more than speculation, based on hindsight knowledge of Applicant's own teachings, that some reagent used in some step of the Rimm et al. or Reiter et al. methods might cause RNA precipitation. As the Federal Circuit has explained, however, "[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient [to establish

inherency.]’ In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981) (citations omitted) (emphasis added). ‘That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.’ In re Spormann, 363 F.2d 444,448, 150 USPQ 449, 452 (CCPA 1966).” In re Rijckaert, 28 USPQ2d at 1957.

In view of the foregoing, independent claim 1 patentably defines over the cited references. The dependent claims recite further patentably distinguishing features. For example, claims 2 and 3 recite preferred species of the RNA preservative.

In reference to claims 2 and 3, the Examiner noted that Rimm et al. teach methyl green as one of a “laundry list” of suitable dyes for use as a stain or counterstain in *in situ* hybridization (Office Action, p. 4 and 5). The Examiner argued that “[a]lthough these authors are silent as regards the RNA preservation properties of this dye, this characteristic is considered to be inherent . . .” (Office Action, p. 4). But the Examiner has failed to cite any motivation for selectively zeroing in on this specific reagent from the laundry list of dyes, let alone from the laundry lists of alternative reagents that may be used in histochemical staining. Nor did the Examiner address the evidence in Applicant’s specification that various reagents used to stain or counterstain biological samples do not preserve or precipitate RNA. Compare, e.g., Example 3(A) on page 33 of the specification, which employed OX42 antibody for staining and Mayer’s Hematoxylin, with Rimm et al., paragraphs 0086 (which lists Hematoxylin) and 0094 (which lists antibodies). It is error to predicate obviousness on an advantage or result flowing from a particular example picked from such a laundry list where the prior art lacks any appreciation of the advantage or result from the selection.

Moreover, the Examiner has failed to cite any specific Rimm et al. or Reiter et al. teaching where a particular reagent is incubated with a biological sample that would necessarily cause RNA to precipitate, which precipitation is performed before histochemical staining and analysis of the sample. Accordingly, even assuming *arguendo*, notwithstanding evidence to the contrary, that each and every histochemical staining reagent disclosed by Rimm et al. or Reiter et al. were to inherently precipitate

RNA, a *prima facie* case of obviousness has not been set forth based on the combination of the Rimm et al. and Reiter et al. references.

The Examiner's further citation of the Lader and Willson III et al. references in further rejecting claim 2 fails to cure the deficiencies of the Rimm et al. and Reiter et al. references. The Examiner indicated that Lader teaches utilizing an RNA preservation medium comprising a salt that precipitates the RNA along with the cellular components in a tissue sample, with one of the exemplified salts being cobalt sulfate. The Examiner further cited Willson III et al. as teaching the use of polyamines, trivalent, and tetravalent metal ions to preserve nucleic acids in a biological sample.

The Examiner, however, failed to explain why an artisan would have been motivated to combine any particular teachings of Lader or Willson III et al. with those of Rimm et al. and Reiter et al., considering that the Lader method pertains to the preservation of RNA in tissue fragments prior to extraction and the Willson et al. method pertains to the use of compaction protection technology to shield nucleic acids during mechanical lysis. In any event, neither reference provides any disclosure or suggestion of precipitating RNA in a biological sample by contacting the biological sample with an aqueous solution comprising an RNA preservative, and then histochemically staining and analyzing the RNA preserved sample, as in the method recited in claim 2. Thus, even assuming *arguendo* that the artisan would have found some motivation to look to these additional references, the presently claimed method would not have been achieved.

As shown above, the Section 103 rejections fail to establish *prima facie* cases of obviousness. The rejections are therefore in error and should be withdrawn.

*Conclusion*

In light of the foregoing, claims 1-4 are allowable and favorable action is therefore requested.

Respectfully submitted,

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